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(71) Applicant: **BP Corporation North America Inc.
Houston, TX 77079 (US)**

(72) Inventor: **BINDER, Joseph B.
Naperville, IL 60563 (US)**

(74) Representative: **Hamer, Christopher K. et al
Mathys & Squire LLP
The Shard
32 London Bridge Street
London SE1 9SG (GB)**

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(54) SYNTHESIS OF FURANS FROM SUGARS VIA KETO INTERMEDIATES

(57) The present invention provides a method of preparing a furan derivative comprising the steps of (a) converting a monosaccharide to provide a keto-intermediate product; and (b) dehydrating the keto-intermediate product to provide a furan derivative; wherein the keto- intermediate product is pre-disposed to forming keto-furanose tautomers in solution. The method may further comprising a step of oxidizing the furan derivative to provide a furandicarboxylic acid or a furandicarboxylic acid derivative.

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a method of preparing a furan derivative via a keto-intermediate product. The method may further comprise a step of oxidizing the furan derivative to provide furandicarboxylic acid or a furandicarboxylic acid derivative.

BACKGROUND OF THE INVENTION

[0002] Five-carbon and six-carbon furans such as furfural and 5-hydroxymethylfurfural may be derived from renewable resources and are promising platform chemicals which may be used in a wide range of applications. For instance, 5-hydroxymethylfurfural may be oxidized into 2,5-furandicarboxylic acid, a component of polyesters resembling polyethylene terephthalate but with improved barrier properties. The challenge of producing furan compounds such as 5-hydroxymethylfurfural in high yield at low cost hinders such applications. 5-hydroxymethylfurfural is traditionally produced from fructose, yet fructose is not as common as other sugars like sucrose and glucose and the pathways are not efficient. Therefore, new routes to furans like 5-hydroxymethylfurfural are needed.

[0003] One of the problems with 5-hydroxymethylfurfural synthesis is that 5-hydroxymethylfurfural itself is not very stable and is difficult to isolate. Therefore routes to furans in which 5-hydroxymethylfurfural is not an isolated intermediate are advantageous.

[0004] Moreover, most routes to bio-based furans use fructose as an intermediate. Glucose is a more common and cheaper sugar, but glucose is either converted into fructose in situ or ex situ to make furans such as 5-hydroxymethylfurfural. Routes to furans which did not require fructose as an intermediate would be advantageous.

SUMMARY OF THE INVENTION

[0005] Therefore what is provided herein is a method of preparing a furan derivative comprising the steps of (a) converting a monosaccharide to provide a keto-intermediate product; and (b) dehydrating the keto-intermediate product to provide a furan derivative, wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution. The method may further comprise a step of oxidizing the furan derivative to provide a furandicarboxylic acid or a furandicarboxylic acid derivative. The furandicarboxylic acid derivative may be a furandicarboxylic acid ester.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006]

Figure 1 shows the conversion of glucose to furandicarboxylic acid through 2-keto-3-deoxygluconic acid as a keto-sugar intermediate;

Figure 2 shows the conversion of glucose to furandicarboxylic acid through 5-keto-D-gluconic acid as a keto-sugar intermediate; and

Figure 3 shows the conversion of glucose to furandicarboxylic acid through 3-deoxy-D-fructose as a keto-sugar intermediate.

Figure 4 shows the conversion of fructose to furandicarboxylic acid through D-lyxo-5-hexosulose as a keto-sugar intermediate.

DETAILED DESCRIPTION OF THE INVENTION

[0007] One of the reasons which makes fructose a key intermediate for production of bio-furans with 2,5-substituents is that fructose has a 2-keto functionality. This 2-keto functionality allows fructose to form keto-furanose tautomers in solution, and these keto-furanose tautomers are pre-disposed to dehydration into 2,5-disubstituted furans.

[0008] In contrast, glucose does not adopt any furanose forms, making it a poor precursor for furan formation. However, there are other sugars which can form furanose tautomers. In fact, sugars such as 2-keto-3-deoxygluconic acid, 2-keto-D-gluconate, 5-keto-D-gluconic acid, D-lyxo-5-hexosulose, and 3-deoxy-D-fructose adopt furanose forms at even higher fractions than fructose, and this pre-disposes them to dehydration into furans.

[0009] The invention takes this insight from the structure of fructose and applies it to non-fructose sugars. In effect, the invention converts other sugars into derivatives which have keto functionality like that of fructose and have a predisposition to form keto-furanose tautomers in solution.

[0010] As shown in Table **1,** NMR spectroscopy measurements show that fructose is present as more than 25% furanose form in water, and this fraction of furanose is even higher in other solvents such as DMSO. In contrast, glucose does not adopt any furanose forms, making it a poor precursor for furan formation. However, there are other sugars which can form furanose tautomers. In fact, sugars such as 2-keto-3-deoxygluconic acid, 2-keto-D-gluconate, 5-keto-D-gluconic acid, 3-deoxy-D-fructose, and D-lyxo-5-hexosulose adopt furanose forms at even higher fractions than fructose, and this pre-disposes them to dehydration into furans.

Table 1. Tautomeric Composition of Sugars in Solution

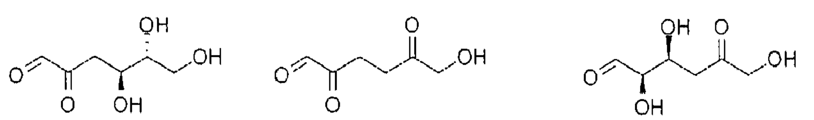
Sugar	Temp. (°C)	Solvent	*keto*	α-pyranose	β-pyranose	α furanose	β furanose	%furanose
D-Fructose	20	D_2O	0.5	2.7	68.2	6.2	22.4	28.6
D-glucose	31	D_2O		38	62			0
2-keto-3-deoxy-D-gluconic acid (KDG)	20	D_2O	0	11	49	23	17	40
D-arabino-2-hexulosonic acid (2-KG)	20	D_2O		73	0	16	11	73
	20	DMSO		36	6	35	23	42
	20	DMF		42	0	36	22	42
Sodium D-xylo-5-hexulosonate (5-KG)	20	D_2O	11			10	79	89
3-deoxy-D-fructose (3-DF)	22	D_2O	7.5	5	52.5	20	15	35
D-lyxo-5-hexosulose		D_2O	8	0	10	14	52	66

[0011] 2-keto-3-deoxygluconic acid, 5-keto-D-gluconic acid, and 2-keto-D-gluconate are the most common 2- or 5-keto sugars which are known to prefer furanose tautomeric forms. 4-deoxy-5-ketoglucaric acid is another example of a 5-keto sugar which occurs naturally. Several keto sugars which prefer furanose forms have been reported in the literature, including 3-deoxy-D-fructose, D-*lyxo*-5-hexulosonic acid, D-lyxo-5-hexosulose, and 4-deoxy-5-ketogalactaric acid. However, there are probably other 2- and 5- keto sugars which prefer furanose tautomeric forms but are not known.

[0012] Many of the 2-keto or 5-keto derivatives may be produced by enzymatic chemistry in high selectivity, including enzymes from the modified Entner-Doudoroff pathway. While it is most likely that the reaction pathway would be practiced with glucose, analogous pathways may be used with other C-6 sugars such as galactose and mannose.

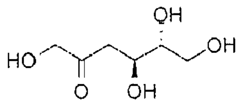
Other dehydration products derived from glucose, sorbitol, or glucose oxidation products which have the 2-keto or 5-keto functionality for dehydration into furans include, but are not limited to, the following:

From glucose:

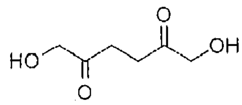


2-keto-3-deoxy-D-glucose 6-hydroxy-2,5-dioxohexanal 4-deoxy-5-keto-D-glucose

From sorbitol:

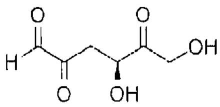


3-deoxy-D-*erythro*-hexulose (3-DF)

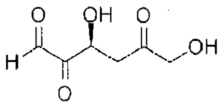


1,6-dihydroxy-2,5-diketohexane

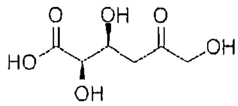
From single oxidation products:



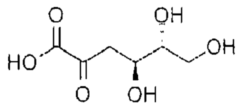
5-keto-D-glucose



2-keto-D-glucose

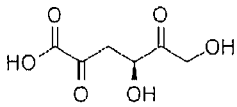


4-deoxy-5-keto-D-gluconic acid

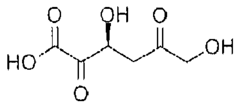


2-keto-3-deoxy-D-gluconic acid

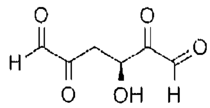
From double oxidation products:



4-Deoxy-5-keto-D-fructuronic acid

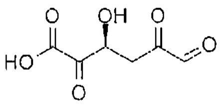


3-Deoxy-5-keto-D-fructuronic acid

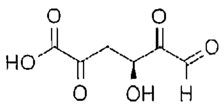


(3*S*)-2,5-dioxo-3-hydroxyhexanedial

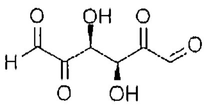
From treble oxidation products:



(3*S*)-3-hydroxy-2,5,6-trioxohexanoic acid



(4*S*)-4-hydroxy-2,5,6-trioxohexanoic acid



(3*S*,4*S*)-3,4-dihydroxy-2,5-dioxohexanedial

[0013] Alternatively, there are some 2- and 5- keto sugars which do not prefer furanose tautomeric forms, including L-sorbose, 5-ketoglucose, L-*xylo*-2-hexulosonic acid, D-glucosone, D-allosone, D-galactosone, and 3-deoxy-D-glucosone. These sugars would not be preferred candidates for dehydration to furans.

[0014] Now therefore, what is provided in a first embodiment is a method of preparing a furan derivative comprising the steps of (a) converting a monosaccharide to provide a keto-intermediate product, and (b) dehydrating the keto-intermediate product to provide a furan derivative, wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution. The method may further comprise a step of oxidizing the furan derivative to provide a furandicarboxylic acid or a furandicarboxylic acid derivative such as, but not limited thereto, a furandicarboxylic acid ester.

[0015] In one embodiment, the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0016] In one embodiment, the monosaccharide is an aldohexose selected from a group consisting of allose, altrose, glucose, mannose, gulose, idose, galactose, and talose. In another embodiment, the monosaccharide is an aldohexose selected from a group consisting of D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, and D-talose.

[0017] In one embodiment, the furan derivative is 5-hydroxymethyl-2-furoic acid.

[0018] In one embodiment the, keto-intermediate product is a 2-keto derivative of the monosaccharide. In another embodiment, the keto-intermediate product is a 5-keto derivative of the monosaccharide. In yet another embodiment, the keto-intermediate product is selected from the group consisting of 3-deoxy-D-fructose, D-lyso-5-hexulosonic acid and 4-deoxy-5-ketogalactactaric acid or any combination thereof.

[0019] In one embodiment, dehydration of the keto-intermediate product occurs by acid catalysis.

[0020] In one embodiment, step (a) of the method comprises oxidation of the monosaccharide to provide an oxidized-product followed by dehydration of the oxidized product to provide a keto-intermediate product, wherein the oxidized product is gluconic acid and wherein the keto-intermediate product is 2-keto-3-deoxygluconic acid.

[0021] In one embodiment, oxidation of the monosaccharide occurs microbially. In another embodiment, oxidation of the monosaccharide occurs enzymatically.

[0022] In one embodiment, dehydration of the oxidized product comprises contacting the oxidized product with an enzyme to provide keto-intermediate product, wherein the enzyme is selected from the group consisting of Galactonate dehydratases having the classification E.C. 4.2.1.6, Altronate dehydratases having the classification E.C. 4.2.1.7, Mannonate dehydratases having the classification E.C. 4.2.1.8, Dihydroxyacid dehydratases having the classification E.C. 4.2.1.9, Gluconate dehydratases having the classification E.C. 4.2.1.39, Glucarate dehydratases having the classification E.C. 4.2.1.40, Galactarate dehydratases having the classification E.C. 4.2.1.42, D-Fuconate dehydratases having the classification E.C. 4.2.1.67, L-Fuconate dehydratases having the classification E.C. 4.2.1.68, Xylonate dehydratases having the classification E.C. 4.2.1.82, Gluconate/galactonate dehydratases having the classification E.C. 4.2.1.140, and L-Galactonate dehydratases having the classification E.C. 4.2.1.146. More specifically, the enzyme is selected from the group consisting of gluconate dehydratase and dihydroxyacid dehydratase or a combination thereof.

[0023] Figure 1 illustrates a possible pathway of the invention utilizing a keto intermediate and its dehydration into a furan. Glucose can be oxidized microbially or enzymatically into gluconic acid. Gluconic acid can be dehydrated by gluconate dehydratase enzymes or dihydroxyacid dehydratase enzymes to form 2-keto-3-deoxygluconic acid, which is a 2-keto sugar which adopts furanose tautomeric forms. Consequently, 2-keto-3-deoxygluconic acid may be dehydrated by acid catalysis into 5-hydroxymethyl-2-furoic acid. 5-hydroxymethyl-2-furoic acid may be oxidized into furandicarboxylic acid using a variety of catalysts for oxidation of aldehydes to acids using a variety of oxidation systems. For example, 5-hydroxymethyl-2-furoic acid may be contacted with an oxygen source, acetic acid solvent, cobalt and manganese oxidation catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours to provide furandicarboxylic acid.

[0024] In one embodiment, step (a) of the method comprises oxidation of the monosaccharide to provide a keto-intermediate product such as, for example but not limited thereto, 5-ketogluconic acid, and step (b) of the method comprises dehydrating the keto-intermediate product to provide a furan derivative such as, for example but not limited thereto, 5-formyl-2-furoic acid.

[0025] Figure 2 illustrates a possible pathway of the invention utilizing a keto intermediate and its dehydration into a furan. Glucose can be oxidized microbially into 5-keto-D-gluconic acid. This acid is a 5-keto sugar which adopts furanose tautomeric forms. Consequently, 5-keto-D-gluconic acid may be dehydrated by acid catalysis into 5-formyl-2-furoic acid. 5-formyl-2-furoic acid may be oxidized into furandicarboxylic acid using a variety of catalysts for oxidation of aldehydes to acids using a variety of oxidation systems. For example, 5-formyl-2-furoic acid may be contacted with an oxygen source, acetic acid solvent, cobalt and manganese oxidation catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours to provide furandicarboxylic acid.

[0026] In one embodiment, step (a) of the method comprises hydrogenation of the monosaccharide to provide a reduced-product followed by dehydration of the reduced product to provide a keto-intermediate product.

[0027] Figure 3 illustrates a possible pathway of the invention utilizing a keto intermediate and its dehydration into a furan. Glucose can be hydrogenated catalytically into sorbitol. If a new enzymatic activity may be found to selectively dehydrate sorbitol to 3-deoxy-D-fructose, then it can be converted into this keto-sugar. This 3-deoxy-D-fructose may be dehydrated by acid catalysis into 2,5-bis(hydroxymethyl)furan. 2,5-bis(hydroxymethyl)furan may be oxidized into furandicarboxylic acid using a variety of catalysts for oxidation of aldehydes to acids using a variety of oxidation systems. For example, 2,5-bis(hydroxymethyl)furan may be contacted with an oxygen source, acetic acid solvent, cobalt and manganese oxidation catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours to provide furandicarboxylic acid,

[0028] In a second embodiment, what is provided is a method of preparing a furan derivative comprising the steps of (a) oxidizing a monosaccharide to provide a keto-intermediate product, and (b) dehydrating the keto-intermediate product to provide a furan derivative; wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0029] In a third embodiment, what is provided is a method of preparing a furan derivative comprising the steps of (a) oxidizing glucose to provide 5-ketogluconic acid, and (b) dehydrating 5-ketogluconic acid to provide 5-formyl-2-furoic acid, wherein 5-ketogluconic acid is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the 5-ketogluconic acid is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0030] In a fourth embodiment, what is provided is a method of preparing a furan derivative comprising the steps of (a) oxidizing a monosaccharide to provide an oxidation product, (b) dehydrating the oxidation product to provide a keto-intermediate product, and (c) dehydrating the keto-intermediate product to provide a furan derivative, wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0031] In a fifth embodiment, what is provided is a method of preparing a furan derivative comprising the steps of (a) oxidizing glucose to provide gluconic acid, (b) dehydrating gluconic acid to provide 2-keto-3-deoxygluconic acid, and (c) dehydrating 2-keto-3-deoxygluconic acid to provide 5-hydroxymethyl-2-furoic acid, wherein 2-keto-3-deoxygluconic acid is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the 2-keto-3-deoxygluconic acid is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0032] In a sixth embodiment what is provided is a method of preparing 2,5-furandicarboxylic acid comprising the steps of (a) oxidizing glucose to provide gluconic acid, (b) dehydrating gluconic acid to provide 2-keto-3-deoxygluconic acid, (c) dehydrating 2-keto-3-deoxygluconic acid to provide 5-hydroxymethyl-2-furoic acid, and (d) oxidizing 5-hydroxymethyl-2-furoic acid to provide 2,5-furandicarboxylic acid, wherein 2-keto-3-deoxygluconic acid is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the 2-keto-3-deoxygluconic acid is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0033] In one embodiment, the glucose of step (a) is contacted with at least one an enzyme to form gluconic acid, wherein the enzyme is selected from the group consisting of glucose oxidase and glucose dehydrogenase or a combination thereof.

[0034] In another embodiment, the glucose of step (a) is oxidized by a microbe to produce gluconic acid, wherein the microbe is selected from the group consisting of *Pseudomonas, Acetobacter, Zymomonas, Gluconobacter, Azospirillum, Aspergillus, Penicillium, Gliocladium, Scopulariopsis, Gonatobotrys, Endomycopsis, Aureobasidium, Tricholoma, and Gluconacetobacter.* More specifically, the microbe is selected from the group consisting of *Pseudomonas ovalis, Pseudomonas savastanoi, Acetobacter methanolicus, Zymomonas mobilis, Acetobacter diazotrophicus, Gluconobacter oxydans, Gluconobacter suboxydans, Azospirillum brasiliense, Aspergillus niger, Penicillium funiculosum, Penicillium glaucum, Penicillium variabile, Penicillium amagasakiense, Aureobasidium pullulans, Tricholoma robustum, Pseudomonas fluorescens, Gluconobacter cerinus, Gluconacetobacter diazotrophicus, Acetobacter aceti, Acetobacter pasteurianus, Acetobacter tropicalis, and Gluconacetobacter xylinus.*

[0035] In one embodiment, the gluconic acid of step (b) is contacted with at least one enzyme to form 2-keto-3-deoxygluconic acid, wherein the enzyme is selected from the group consisting of Galactonate dehydratases having the classification E.C. 4.2.1.6, Altronate dehydratases having the classification E.C. 4.2.1.7, Mannonate dehydratases having the classification E.C. 4.2.1.8, Dihydroxyacid dehydratases having the classification E.C. 4.2.1.9, Gluconate dehydratases having the classification E.C. 4.2.1.39, Glucarate dehydratases having the classification E.C. 4.2.1.40, Galactarate dehydratases having the classification E.C. 4.2.1.42, D-Fuconate dehydratases having the classification E.C. 4.2.1.67, L-Fuconate dehydratases having the classification E.C. 4.2.1.68, Xylonate dehydratases having the classification E.C. 4.2.1.82, Gluconate/galactonate dehydratases having the classification E.C. 4.2.1.140, and L-Galactonate dehydratases having the classification E.C. 4.2.1.146. More specicifcally, the enzyme is selected from the group consisting of gluconate dehydratase and dihydroxy-acid dehydratase.

[0036] In one embodiment, the 2-keto-3-deoxygluconic acid of step (c) undergoes acid catalysed dehydration by contacting the 2-keto-3-deoxygluconic acid with an acid to provide 5-hydroxymethyl-2-furoic acid, wherein the acid is selected from the group consisting of acetic acid, sulphuric acid, trifluoroacetic acid, hydrobromic acid, hydrochloric acid, and hydroiodic acid or any combination thereof. In one embodiment, the 2-keto-3-deoxygluconic acid in step (c) is subjected to acid catalysed dehydration by contacting the 2-keto-3-deoxygluconic acid with an acid and heated to a temperature in the range of about 10°C to about 200°C for a period of time of about 5 minutes to about 10 hours to provide 5-hydroxymethyl-2-furoic acid. In one embodiment, the acid is selected from the group consisting of acetic acid, sulphuric acid, trifluoroacetic acid, hydrobromic acid, hydrochloric acid, and hydroiodic acid or any combination thereof.

[0037] In one embodiment, the 5-hydroxymethyl-2-furoic acid of step (d) is oxidized to 2,5-furandicarboxylic acid by contacting the 5-hydroxymethyl-2-furoic acid with an oxygen source, acetic acid solvent, cobalt and manganese oxidation catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours.

[0038] In a seventh embodiment, what is provided is a method of preparing a furan derivative comprising the steps of (a) hydrogenating a monosaccharide to provide a reduced-product, (b) dehydrating the reduced-product to provide a keto-intermediate product, and (c) dehydrating the keto-intermediate product to provide a furan derivative, wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0039] In an eighth embodiment, what is provided is a method of preparing a furan derivative comprising the steps of (a) hydrogenating glucose to provide sorbitol, (b) dehydrating sorbitol to provide 3-deoxy-D-fructose, and (c) dehydrating

3-deoxy-D-fructose to provide 2,5-bis(hydroxymethyl)furan, wherein 3-deoxy-D-fructose is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the 3-deoxy-D-fructose is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0040] In a ninth embodiment, what is provided is a method of preparing 2,5-furandicarboxylic acid comprising the steps of (a) hydrogenating glucose to provide sorbitol, (b) dehydrating sorbitol to provide 3-deoxy-D-fructose, (c) dehydrating 3-deoxy-D-fructose to provide 2,5-bis(hydroxymethyl)furan, and (d) oxidizing 2,5-bis(hydroxymethyl)furan to provide 2,5-furandicarboxylic acid, wherein 3-deoxy-D-fructose is pre-disposed to forming keto-furanose tautomers in solution. In one embodiment, the 3-deoxy-D-fructose is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example but not limited thereto, water at a temperature of about 25°C.

[0041] In a tenth embodiment, what is provided is a method of preparing a furan derivative comprising the steps of, (a) oxidizing fructose to provide D-lyxo-5-hexosulose, and (b) dehydrating D-lyxo-5-hexosulose to provide 2,5-diformylfuran, wherein the D-lyxo-5-hexosulose is pre-disposed to forming keto-furanose tautomers in solution.

[0042] In one embodiment, the method further comprises the step of oxidizing 2,5-diformylfuran to provide 2,5-furandicarboxylic acid. For example, 2,5-diformylfuran may be contacted with an oxygen source, acetic acid solvent, cobalt and manganese oxidation catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours to provide furandicarboxylic acid.

[0043] In one embodiment, the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution such as, for example, but not limited thereto, water at a temperature of about 25°C.

EXAMPLES

Reagents

[0044] 2-keto-3-deoxygluconic acid lithium salt hydrate, potassium 5-keto-D-gluconate, calcium 2-keto-D-gluconate hemihydrate, hydrogen bromide in acetic acid (33 wt %, HBr/HOAc), Hydrogen bromide in water (48 wt %, HBr), trifluoroacetic acid (TFA), acetic anhydride (Ac_2O), acetic acid, sulfuric acid (98% in water, H_2SO_4), and hydroiodic acid (57% in water, HI) were obtained from Sigma-Aldrich.

Example 1: Oxidation of Glucose into 5-keto-D-gluconic acid

[0045] Glucose (20 g), polypeptone (2 g), and yeast extract (1 g) are mixed in 1 L of deionized water, and this medium is placed in a fermentation tank. The tank is inoculated with a culture of *Gluconobacter suboxydans* IFO 12528 and agitated and aerated at 30°C for 170 hours with pH maintained at pH 3.5 by controlled addition of sodium hydroxide. During the fermentation, glucose is converted to sodium 5-ketogluconate with traces of sodium gluconate and sodium 2-ketogluconate.

Example 2: Oxidation of Glucose into 2-keto-D-gluconate

[0046] Glucose (100 g), corn steep liquor (5 g), urea (2 g), $MgSO_4$ heptahydrate (0.25 g), KH_2PO_4 (0.6 g), and $CaCO_3$ (27 g) are mixed in 1 L of deionized water, and this medium is placed in a fermentation tank. The tank is inoculated with a culture of *Pseudomonas fluorescens,* and agitated and aerated at 25°C for 43 hours. During the fermentation, glucose is converted to calcium 2-ketogluconate.

Example 3: Oxidation of Glucose into Gluconate

[0047] Glucose (100 g) and yeast extract (10 g) are mixed in 1 L of deionized water, and this medium is divided amongst several shake flasks. Each flask containing medium is inoculated with a culture of *Gluconobacter oxydans,* and incubated at 32°C for 8 hours in a shaker with good agitation for medium aeration. During the fermentation, glucose is converted to gluconate and gluconic acid.

Example 4: Dehydration of Gluconate into 2-keto-3-deoxygluconic acid

[0048] The dihydroxyacid dehydratase from *Sulfolobus solfataricus* (Kim, S; Lee, S.B. "Catalytic Promiscuity in Dihydroxy-Acid Dehydratase from the Thennoacidophilic Archaeon Sulfolobus solfataricus." Journal of Biochemistry, 2006, 139, 591-596) was expressed in *E. coli.* The gene was synthesized, cloned into a vector, and transformed into *E. coli.* Transformed *E. coli* were grown on a shake flask scale to express the heterologous dihydroxyacid dehydratase protein. On completion of the fermentation, protein was extracted using a detergent extraction reagent and clarified protein extracts were produced. Gluconate dehydration reactions were performed by combining the clarified cell extract in a 1:1 volume ratio with 50 mM Tris HCl buffer containing 40 mM sodium gluconate (measured pH 8.35). These were incubated at 60°C for 24.75 hours and analyzed by liquid chromatography for conversion of gluconate. Nearly all of the gluconate was converted to a new product. For positive identification of the 2-keto-3-deoxygluconic acid product, proton NMR was used. Comparison of the spectra of the enzymatic reaction samples show that gluconate has disappeared from the reaction mixture and new peaks corresponding to the reported spectrum of 2-keto-3-deoxygluconic acid have appeared (reported spectrum from Plantier-Royon, R.; Cardona, F.; Anker, D.; Condemine, G.; Nasser, W.; Robert-Baudouy, J. Nouvelle Synthese de L'Acide 3-Desoxy-D-Erythro-2-Hexulosonique. J. Carbohydrate Chem. 1991, 10, 787-811).

Example 5: Hydrogenation of Glucose into Sorbitol

[0049] Glucose is dissolved in water to produce a 40 wt % glucose solution, and the solution is adjusted to pH 8 using sodium hydroxide. The glucose solution is contacted with hydrogen gas at a hydrogen partial pressure of 2000 psig in the presence of Raney nickel catalyst at a temperature of 140°C. Under these conditions, glucose is converted to sorbitol in near quantitative yield.

Example 6: Dehydration of Sorbitol into 3-Deoxyfructose

[0050] Sorbitol is dissolved in 50 mM Tris HCl buffer to which a clarified cell extract containing dehydratase enzyme of class 4.2.1 is added. This mixture is incubated at 30°C for 24 hours. Sorbitol is converted into 3-deoxyfructose.

Examples 7-18: Dehydration of 2-keto-3-deoxygluconic acid into 5-hydroxymethyl-2-furoic acid

[0051] 2-keto-3-deoxygluconic acid was dissolved in water and acetic acid by placing 8.45 mg of 2-keto-3-deoxygluconic acid in a very small sample vial. To this was added 120 ul of water and 120 ul of acetic acid, and this was mixed to dissolve the 2-keto-3-deoxygluconic acid. This stock solution was used for each reaction according to Table 2. In each case, 20 ul of the 2-keto-3-deoxygluconic acid solution was added first to a vial along with a mini stir bar. The remaining reagents were added in the order shown in Table 2 (left to right) and mixed by stirring on a stirplate. Each vial was capped and heated to 60°C with stirring. After the reaction time, the vial contents were cooled and analyzed for 5-hydroxymethyl-2-furoic acid by HPLC.

Table 2. Dehydration of 2-keto-3-deoxygluconic acid and yield of 5-hydroxymethyl-2-furoic acid

#	Ac_2O (ul)	Acetic (ul)	HBr/HOAc (ul)	H_2O (ul)	Acid (ul)	Time (h)	Yield (mol %)
7	-	365	375	-	-	4	12
8	-	-	740	-	-	4	7
9	405	299	-	-	H_2SO_4, 36	4	<5
10	365	-	375	-	-	4	6
11	364	263	113	-	-	4	6
12	-	-	675	65	-	4	<5
13	-	337	338	65	-	4	10
14	-	-	-	-	TFA, 740	4	45
15				683	TFA, 57	1	21
16				700	H_2SO_4, 40	1	15
17				655	HBr, 85	1	9
18				641	HI, 99	1	<5

Examples 19-39: Dehydration of 5-keto-D-gluconic acid into 5-hydroxymethyl-2-furoic acid and 5-formyl-2-furoic acid

[0052] Potassium 5-keto-D-gluconate (70 mg) was placed in a vial along with a mini stir bar. The other reagents in Table 3 were added to the vial in order from left to right and mixed by stirring on a stirplate. Each vial was capped and heated to the reaction temperature with stirring. After the reaction time, the vial contents were cooled and analyzed for furans by HPLC.

Table 3. Dehydration of 5-keto-D-gluconic acid into 5-hydroxymethyl-2-furoic acid (HMFA) and 5-formyl-2-furoic acid (FFA)

#	5-KG (mg)	LiBr (mg)	H_2O (ul)	Ac_2O (ul)	Acetic (ul)	Acctic/HBr (ul)	Otheracid (ul)	Temp. (°C)	Time (h)	HMFA %	FFA %
19	70		242			2700		100	2	0.04	
20	70				1500		1500, H_2SO_4	100	2		
21	70				1500		1500, MSA	100	2		
22	70			1430	1430	-	142, H_2SO_4	100	2		0.7
23	70						3000, 48% HBr	100	2		
24	70		242				2700, H_2SO_4	100	2		
25	70						3000, HCl	100	2		
26	70						3000, TFA	100	2		0.2
27	70		2700				230, TFA	100	2		
28	140	2002	446				1260, 48% HBr	100	2		
29	70		242			2700		60	4	6.9	0.03
30	70				1500		1500, H_2SO_4	60	4		0,01
31	70				1500		1500, MSA	60	4		0.04
32	70			1430	1430	-	142, H_2SO_4	60	4		0.75
33	70						3000, 48% HBr	60	4		3.42
34	70		242				2700, H_2SO_4	60	4		0.20
35	70						3000, HCl	60	4		0.96
36	70						3000, TFA	60	4		
37	70		2700				230, TFA	60	4		0.21
38	140	2002	446				1260, 48% HBr	60	4		
39	70				3000			100	2		1.7

Note: Acetic acid/HBr refers to 33 wt % HBr in acetic acid. H_2SO_4 refers to 98% sulfuric acid. TFA is trifluoroacetic acid. Ac_2O is acetic anhydride. HCl is 37% concentrated hydrochloric acid. 48% HBr is 48% hydrobromic acid in water. MSA is methanesulfonic acid.

Examples 40-43: Dehydration of 2-keto-D-gluconate into 5-hydroxymethyl-2-furoic acid and 5-formyl-2-furoic acid

[0053] Calcium 2-keto-D-gluconate hemihydrate (64 mg) was placed in a vial along with a mini stir bar. The other reagents in Table 4 were added to the vial in order from left to right. and mixed by stirring on a stirplate. Each vial was capped and heated to the reaction temperature with stirring. After the reaction time, the vial contents were cooled and analyzed for furans by HPLC.

Table 4. Dehydration of 2-keto-D-gluconate into 5-hydroxymethyl-2-furoic acid (HMFA) and 5-formyl-2-furoic acid (FFA)

#	2-KG (mg)	LiBr (mg)	H_2O (ul)	Ac_2O (ul)	Acetic (ul)	Acetic/HBr (ul)	Other acid (ul)	Temp. (°C)	Time (h)	HMFA %	FFA %
40	70				3000			100	2	0.19	0.19
41	70				3000		58, H_2SO_4	100	2		0.13
42	70		242			2700		60	4	18.9	
43	70						3000, HCl	60	4		0.81
Note: Acetic acid/HBr refers to 33 wt % HBr in acetic acid. H_2SO_4 refers to 98% sulfuric acid. HCl is 37% concentrated aqueous hydrochloric acid.											

Examples 44-55: Dehydration of 3-Deoxyfructose into 2,5-bis(hydroxymethyl)furan

[0054] 3-deoxy-D-fructose is dissolved in water by placing 10 mg of 3-deoxy-D-fructose in a very small sample vial. To this is added 250 ul of water, and this is mixed to dissolve the 3-deoxy-D-fructose. This stock solution is used for each reaction according to Table 5. In each case, 20 ul of the 3-deoxy-D-fructose solution is added first to a vial along with a mini stir bar. The remaining reagents are added in the order shown in Table 5 (left to right) and mixed by stirring on a stirplate. Each vial is capped and heated to 60°C with stirring. After the reaction time, the vial contents are cooled and analyzed for 2,5-bis(hydroxymethyl)furan by HPLC analysis. Conversion of 3-deoxy-D-fructose into 2,5-bis(hydroxymethyl)furan is observed.

Table 5. Dehydration of 3-deoxy-D-fructose to form 2,5-bis(hydroxymethyl)furan

#	Ac_2O (ul)	Acetic (ul)	HBr/HOAc (ul)	H_2O (ul)	Acid (ul)	Time (h)
44	-	365	375	-	-	4
45	-	-	740	-	-	4
46	405	299	-	-	H_2SO_4, 36	4
47	365	-	375	-	-	4
48	364	263	113	-	-	4
49	-	-	675	65	-	4
50	-	337	338	65	-	4
51	-	-	-	-	TFA, 740	4
52				683	TFA, 57	1
53				700	H_2SO_4, 40	1
54				655	HBr, 85	1
55				641	HI, 99	1

Example 56: Oxidation of 5-hydroxymethyl-2-furoic acid into furandicarboxylic acid

[0055] 5-hydroxymethyl-2-furoic acid (2.5 g), acetic acid (30 ml), cobalt acetate (0.083 g), sodium bromide (0.071 g), and manganese acetate (0.084 g) are mixed in a batch reactor and placed under an excess of oxygen at 800 psig with vigorous mixing for 1 hour at 180°C. LC analysis of the total reaction mixture shows conversion of 5-hydroxymethyl-2-furoic acid to furandicarboxylic acid.

Example 57: Oxidation of 5-formyl-2-furoic acid into furandicarboxylic acid

[0056] 5-formyl-2-furoic acid (2.5 g), acetic acid (30 ml), cobalt acetate (0.083 g), sodium bromide (0.071 g), and manganese acetate (0.084 g) are mixed in a batch reactor and placed under an excess of oxygen at 800 psig with vigorous mixing for 1 hour at 180°C. LC analysis of the total reaction mixture shows conversion of 5-formyl-2-furoic acid to furandicarboxylic acid.

Example 58: Oxidation of 2,5-bis(hydroxymethyl)furan into furandicarboxylic acid

[0057] 2,5-bis(hydroxymethyl)furan (2.5 g), acetic acid (30 ml), cobalt acetate (0.083 g), sodium bromide (0.071 g), and manganese acetate (0.084 g) are mixed in a batch reactor and placed under an excess of oxygen at 800 psig with vigorous mixing for 1 hour at 180°C. LC analysis of the total reaction mixture shows conversion of 2,5-bis(hydroxymethyl)furan to furandicarboxylic acid.

Example 59: Oxidation of Fructose into D-lyxo-5-hexosulose

[0058] Fructose (100 g) and yeast extract (10 g) are mixed in 1 L of deionized water, and this medium is divided amongst several shake flasks. Each flask containing medium is inoculated with a culture of *Gluconobacter oxydans,* and incubated at 32°C for 8 hours in a shaker with good agitation for medium aeration. During the fermentation, fructose is converted to D-*lyxo*-5-hexosulose.

Examples 60-71: Dehydration of D-lyxo-5-hexosulose into 2,5-diformylfuran

[0059] D-*lyxo*-5-hexosulose is dissolved in water by placing 10 mg of D-*lyxo*-5-hexosulose in a very small sample vial. To this is added 250 ul of water, and this is mixed to dissolve the D-*lyxo*-5-hexosulose. This stock solution is used for each reaction according to Table 6. In each case, 20 ul of the D-*lyxo*-5-hexosulose solution is added first to a vial along with a mini stir bar. The remaining reagents are added in the order shown in Table 6 (left to right) and mixed by stirring on a stirplate. Each vial is capped and heated to 60°C with stirring. After the reaction time, the vial contents are cooled and analyzed for 2,5-bis(hydroxymethyl)furan by HPLC analysis. Conversion of D-*lyxo*-5-hexosulose into 2,5-diformylfuran is observed.

Table 6. Dehydration of D-*lyxo*-5-hexosulose to form 2,5-diformylfuran

#	Ac_2O (ul)	Acetic (ul)	HBr/HOAc (ul)	H_2O (ul)	Acid (ul)	Time (h)
60	-	365	375	-	-	4
61	-	-	740	-	-	4
62	405	299	-	-	H_2SO_4, 36	4
63	365	-	375	-	-	4
64	364	263	113	-	-	4
65	-	-	675	65	-	4
66	-	337	338	65	-	4
67	-	-	-	-	TFA, 740	4
68				683	TFA, 57	1
69				700	H_2SO_4, 40	1
70				655	HBr, 85	1
71				641	HI, 99	1

Example 72: Oxidation of 2,5-diformylfuran into furandicarboxylic acid

[0060] 2,5-diformylfuran (2.5 g), acetic acid (30 ml), cobalt acetate (0.083 g), sodium bromide (0.071 g), and manganese acetate (0.084 g) are mixed in a batch reactor and placed under an excess of oxygen at 800 psig with vigorous mixing for 1 hour at 180°C. LC analysis of the total reaction mixture shows conversion of 2,5-diformylfuran to furandicarboxylic acid.

[0061] The invention is also described by reference to the following clauses:

1. A method of preparing a furan derivative comprising the steps of:

   a. converting a monosaccharide to provide a keto-intermediate product; and
   b. dehydrating the keto-intermediate product to provide a furan derivative;

   wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution.

2. The method of clause 1, wherein the monosaccharide is an aldohexose.

3. The method of clause 2, wherein the aldohexose is selected from a group consisting of allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.

4. The method of clause 2, wherein the aldohexose is selected from a group consisting of D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, and D-talose.

5. The method of clause 1 further comprising a step of oxidizing the furan derivative to provide a furandicarboxylic acid or a furandicarboxylic acid derivative.

6. The method of clause 5, wherein the furandicarboxylic acid derivative is furandicarboxylic acid ester.

7. The method of clause 1, wherein step (a) comprises oxidation of the monosaccharide to provide a keto-intermediate product.

8. The method of clause 1, wherein step (a) comprises oxidation of the monosaccharide to provide an oxidized-product followed by dehydration of the oxidized product to provide a keto-intermediate product.

9. The method of clause8, wherein the oxidized product is gluconic acid.

10. The method of clause 8, wherein the keto-intermediate product is 2-keto-3-deoxygluconic acid.

11. The method of clause 1, wherein the furan derivative is 5-hydroxymethyl-2-furoic acid.

12. The method of clause 7, wherein the keto-intermediate product is 5-ketogluconic acid.

13. The method of clause 12, wherein the furan derivative is 5-formyl-2-furoic acid.

14. The method of clause 1, wherein the keto-intermediate product is a 2-keto derivative of the monosaccharide.

15. The method of clause 1, wherein the keto-intermediate product is a 5-keto derivative of the monosaccharide.

16. The method of clause 8, wherein oxidation of the monosaccharide occurs microbially.

17. The method of clause 8, wherein oxidation of the monosaccharide occurs enzymatically.

18. The method of clause 1, wherein the dehydration of the keto-intermediate product occurs by acid catalysis.

19. The method of clause 8, wherein dehydration of the oxidized product comprises contacting the oxidized product with an enzyme to provide keto-intermediate product.

20. The method of clause 19, wherein the enzyme is selected from the group consisting of Galactonate dehydratases

having the classification E.C. 4.2.1.6, Altronate dehydratases having the classification E.C. 4.2.1.7, Mannonate dehydratases having the classification E.C. 4.2.1.8, Dihydroxyacid dehydratases having the classification E.C. 4.2.1.9, Gluconate dehydratases having the classification E.C. 4.2.1.39, Glucarate dehydratases having the classification E.C. 4.2.1.40, Galactarate dehydratases having the classification E.C. 4.2.1.42, D-Fuconate dehydratases having the classification E.C. 4.2.1.67, L-Fuconate dehydratases having the classification E.C. 4.2.1.68, Xylonate dehydratases having the classification E.C. 4.2.1.82, Gluconate/galactonate dehydratases having the classification E.C. 4.2.1.140, and L-Galactonate dehydratases having the classification E.C. 4.2.1.146.

21. The method of clause 19, wherein the enzyme is selected from the group consisting of gluconate dehydratase and dihydroxyacid dehydratase or a combination thereof.

22. The method of clause 1, wherein step (a) comprises hydrogenation of the monosaccharide to provide a reduced-product followed by dehydration of the reduced product to provide a keto-intermediate product.

23. The method of clause 1, wherein the keto-intermediate product is selected from the group consisting of 3-deoxy-D-fructose, D-lyso-5-hexulosonic acid and 4-deoxy-5-ketogalactactaric acid or any combination thereof.

24. A method of preparing 2,5-furandicarboxylic acid derivative comprising the steps of:

a. oxidizing glucose to provide gluconic acid;
b. dehydrating gluconic acid to provide 2-keto-3-deoxygluconic acid;
c. dehydrating 2-keto-3-deoxygluconic acid to provide 5-hydroxymethyl-2-furoic acid; and
d. oxidizing 5-hydroxymethyl-2-furoic acid to provide 2,5-furandicarboxylic acid;

wherein 2-keto-3-deoxygluconic acid is pre-disposed to forming keto-furanose tautomers in solution.

25. The method of clause 24, wherein the glucose of step (a) is contacted with at least one enzyme to form gluconic acid.

26. The method of clause 25, wherein the enzyme is selected from the group consisting of glucose oxidase and glucose dehydrogenase or a combination thereof.

27. The method of clause 24, wherein the glucose of step (a) is oxidized by a microbe to produce gluconic acid.

28. The method of clause 27, wherein the microbe is selected from the group consisting of *Pseudomonas, Acetobacter, Zyrnomonas, Gluconobacter, Azospirillum, Aspergillus, Penicillium, Gliocladium, Scopulariopsis, Gonatobotrys, Endomycopsis, Aureobasidium, Tricholoma, and Gluconacetobacter,*

29. The method of clause 27, wherein the microbe is selected from the group consisting of *Pseudomonas ovalis, Pseudomonas savastanoi, Acetobacter methanolicus, Zymomonas mobilis, Acetobacter diazotrophicus, Gluconobacter oxydans, Gluconobacter suboxydans, Azospirillum brasiliense, Aspergillus niger, Penicillium funiculosum, Penicillium glaucum, Penicillium variabile, Penicillium amagasakiense, Aureobasidium pullulans, Tricholoma robustum, Pseudomonas fluorescens, Gluconobacter cerinus, Gluconacetobacter diazotrophicus, Acetobacter aceti, Acetobacter pasteurianus, Acetobacter tropicalis, and Gluconacetobacter xylinus.*

30. The method of clause 24, wherein the gluconic acid of step (b) is contacted with at least one enzyme to form 2-keto-3-deoxygluconic acid.

31. The method of clause 30, wherein the enzyme is selected from the group consisting of Galactonate dehydratases having the classification E.C. 4.2.1.6, Altronate dehydratases having the classification E.C. 4.2.1.7, Mannonate dehydratases having the classification E.C. 4.2.1.8, Dihydroxyacid dehydratases having the classification E.C. 4.2.1.9, Gluconate dehydratases having the classification E.C. 4.2.1.39, Glucarate dehydratases having the classification E.C. 4.2.1.40, Galactarate dehydratases having the classification E.C. 4.2.1.42, D-Fuconate dehydratases having the classification E.C. 4.2.1.67, L-Fuconate dehydratases having the classification E.C. 4.2.1.68, Xylonate dehydratases having the classification E.C. 4.2.1.82, Gluconate/galactonate dehydratases having the classification E.C. 4.2.1.140, and L-Galactonate dehydratases having the classification E.C. 4.2.1.146.

32. The method of clause 30, wherein the enzyme is selected from the group consisting of gluconate dehydratase

and dihydroxy-acid dehydratase.

33. The method of clause 24, wherein the 2-keto-3-deoxygluconic acid of step (c) undergoes acid catalysed dehydration by contacting the 2-keto-3-deoxygluconic acid with an acid to provide 5-hydroxymethyl-2-furoic acid.

34. The method of clause 33, wherein the acid is selected from the group consisting of acetic acid, sulphuric acid, trifluoroacetic acid, hydrobromic acid, hydrochloric acid, and hydroiodic acid or any combination thereof.

35. The method of clause 34, wherein the 2-keto-3-deoxygluconic acid in step (c) is subjected to acid catalysed dehydration by contacting the 2-keto-3-deoxygluconic acid with an acid and heated to a temperature in the range of about 10°C to about 200°C for a period of time of about 5 minutes to about 10 hours to provide 5-hydroxymethyl-2-furoic acid.

36. The method of clause 35, wherein the acid is selected from the group consisting of acetic acid, sulphuric acid, trifluoroacetic acid, hydrobromic acid, hydrochloric acid, and hydroiodic acid or any combination thereof.

37. The method of clause 23, wherein the 5-hydroxymethyl-2-furoic acid of step (d) is oxidized to 2,5-furandicarboxylic acid by contacting the 5-hydroxymethyl-2-furoic acid with an oxygen source, acetic acid solvent, cobalt and manganese oxidation catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours.

38. The method of clause 27, wherein the microbe is *Aspergillus niger.*

39. A method of preparing 2,5-furandicarboxylic acid comprising the steps of:

a. oxidizing glucose to provide 5-ketogluconic acid;
b. dehydrating 5-ketogluconic acid to provide 5-formyl-2-furoic acid; and
c. oxidizing 5-formyl-2-furoic acid to provide 2,5-furandicarboxylic acid;

wherein 5-ketogluconic acid is pre-disposed to forming keto-furanose tautomers in solution.

40. The method of clause 39, wherein glucose is oxidized by a microbe to provide 5-ketogluconic acid.

41. The method of clause 39, wherein the microbe is selected from the group consisting of *Pseudomonas, Acetobacter, Zymomonas. Gluconobacter, Azospirillum, Aspergillus, Penicillium, Gliocladium, Scopulariopsis, Gonatobotrys. Endomycopsis, Aureobasidium, Tricholoma, and Gluconacetobacter.*

42. The method of clause 39, wherein the microbe is selected from the group consisting of *Pseudomonas ovalis, Pseudomonas savastanoi, Acetobacter methanolicus, Zymomonas mobilis, Acetobacter diazotrophicus, Gluconobacter oxydans, Gluconobacter suboxydans, Azospirillum brasiliense, Aspergillus niger, Penicillium funiculosum, Penicillium glaucum, Penicillium variabile, Penicillium amagasakiense, Aureobasidium pullulans, Tricholoma robustum, Pseudomonas fluorescens, Gluconobacter cerinus, Gluconacetobacter diazotrophicus, Acetobacter aceti, Acetobacter pasteurianus, Acetobacter tropicalis, and Gluconacetobacter xylinus.*

43. The method of clause 39, wherein the microbe is selected from the group consisting of *Pseudomonas ovalis, Pseudomonas savastanoi, Acetobacter methanolicus, Acetobacter diazotrophicus, Gluconobacter oxydans, Gluconobacter suboxydans, Pseudomonas fluorescens, Gluconobacter cerinus, Gluconacetobacter diazotrophicus, Acetobacter aceti, Acetobacter pasteurianus, Acetobacter tropicalis, and Gluconacetobacter xylinus.*

44. The method of clause 39, wherein 5-ketogluconic acid in step (b) is subjected to acid catalysed dehydration by contacting the 5-ketogluconic acid with an acid and heated to a temperature in the range of about 10°C to about 200°C for a period of time of about 5 minutes to about 10 hours to provide 5-formyl-2-furoic acid.

45. The method of clause 44, wherein the acid is selected from the group consisting of acetic acid, sulphuric acid, trifluoroacetic acid, hydrobromic acid, hydroiodic acid, hydrochloric, methanesulfonic acid or any combination thereof.

46. The method of clause 39, wherein the 5-formyl-2-furoic acid in step (c) is oxidized to 2,5-furandicarboxylic acid by contacting the 5-formyl-2-furoic acid with an oxygen source, acetic acid solvent, cobalt and manganese oxidation

catalyst, a bromine source, at a temperature in the range of about 50°C to about 200°C, and a pressure in the range of about 1 bar to about 100 bar for a period of time from about 1 minutes to about 10 hours.

47. A method of preparing 2,5-furandicarboxylic acid comprising the steps of:

a. hydrogenating glucose to provide sorbitol;
b. dehydrating sorbitol to provide 3-deoxy-D-fructose;
c. dehydrating 3-deoxy-D-fructose to provide 2,5-bis(hydroxymethyl)furan; and
d. oxidizing 2,5-bis(hydroxymethyl)furan to provide 2,5-furandicarboxylic acid;

wherein 3-deoxy-D-fructose is pre-disposed to forming keto-furanose tautomers in solution.

48. A method of preparing a furan derivative comprising the steps of:

a. oxidizing glucose to provide gluconic acid;
b. dehydrating gluconic acid to provide 2-keto-3-deoxygluconic acid; and
c. dehydrating 2-keto-3-deoxygluconic acid to provide 5-hydroxymethyl-2-furoic acid;

wherein 2-keto-3-deoxygluconic acid is pre-disposed to forming keto-furanose tautomers in solution.

49. A method of preparing a furan derivative comprising the steps of:

a. oxidizing glucose to provide 5-ketogluconic acid; and
b. dehydrating 5-ketogluconic acid to provide 5-formyl-2-furoic acid;

wherein 5-ketogluconic acid is pre-disposed to forming keto-furanose tautomers in solution.

50. A method of preparing a furan derivative comprising the steps of:

a. hydrogenating glucose to provide sorbitol;
b. dehydrating sorbitol to provide 3-deoxy-D-fructose; and
c. dehydrating 3-deoxy-D-fructose to provide 2,5-bis(hydroxymethyl)furan;

wherein 3-deoxy-D-fructose is pre-disposed to forming keto-furanose tautomers in solution.

51. A method of preparing a furan derivative comprising the steps of:

a. oxidizing a monosaccharide to provide an oxidation product;
b. dehydrating the oxidation product to provide a keto-intermediate product; and
c. dehydrating the keto-intermediate product to provide a furan derivative;

wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution.

52. A method of preparing a furan derivative comprising the steps of:

a. oxidizing a monosaccharide to provide a keto-intermediate product; and
b. dehydrating the keto-intermediate product to provide a furan derivative;

wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution.

53. A method of preparing a furan derivative comprising the steps of:

a. hydrogenating a monosaccharide to provide a reduced-product;
b. dehydrating the reduced-product to provide a keto-intermediate product; and
c. dehydrating the keto-intermediate product to provide a furan derivative;

wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution.

54. A method of preparing a furan derivative comprising the steps of:

a. oxidizing fructose to provide D-lyxo-5-hexosulose; and
b. dehydrating D-lyxo-5-hexosulose to provide 2,5-diformylfuran;

wherein the D-lyxo-5-hexosulose is pre-disposed to forming keto-furanose tautomers in solution.

55. The method of clause 54 further comprising the step of oxidizing 2,5-diformylfuran to provide 2,5-furandicarboxylic acid.

56. The method of clause 1, wherein the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution.

57. The method of clause 56, wherein the solution is water at a temperature of about 25°C.

Claims

1. A method of preparing a furan derivative comprising the steps of:

a. converting a monosaccharide to provide a keto-intermediate product; and
b. dehydrating the keto-intermediate product to provide a furan derivative;

wherein the keto-intermediate product is pre-disposed to forming keto-furanose tautomers in solution.

2. The method of claim 1, wherein the keto-intermediate product is pre-disposed to forming at least 30% keto-furanose tautomers in solution.

3. The method of claim 2, wherein the solution is water at a temperature of about 25°C.

4. The method of claim 1, wherein the keto-intermediate product is selected from 2-keto-3-deoxygluconic acid, 2-ketogluconate, 5-ketogluconic acid, 3-deoxy-D-fructose, D-lyxo-5-hexosulose, D-lyxo-5-hexulosonic acid, and 4-deoxy-5-ketogalactaric acid.

5. The method of claim 1, wherein the keto-intermediate product is 2-keto-3-deoxygluconic acid, 5-keto-D-gluconic acid, 3-deoxy-D-fructose, or D-lyxo-5-hexosulose; or wherein the keto-intermediate product is 2-keto-3-deoxygluconic acid or 5-keto-D-gluconic acid.

6. The method of claim 1, wherein the monosaccharide is an aldohexose selected from a group consisting of allose, altrose, glucose, mannose, gulose, idose, galactose, and talose; or wherein the monosaccharide is an aldohexose selected from a group consisting of D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, and D-talose.

7. The method of claim 1, wherein the dehydration of the keto-intermediate product occurs by acid catalysis.

8. The method of claim 1 further comprising a step of oxidizing the furan derivative to provide a furandicarboxylic acid or a furandicarboxylic acid derivative.

9. The method of claim 8, wherein the furandicarboxylic acid derivative is furandicarboxylic acid ester.

10. The method of claim 1, wherein step (a) comprises oxidation of the monosaccharide to provide a keto-intermediate product;
or wherein step (a) comprises oxidation of the monosaccharide to provide an oxidized-product followed by dehydration of the oxidized product to provide a keto-intermediate product; or
or wherein step (a) comprises hydrogenation of the monosaccharide to provide a reduced-product followed by dehydration of the reduced product to provide a keto-intermediate product.

11. The method of claim 10, wherein the oxidized product is gluconic acid.

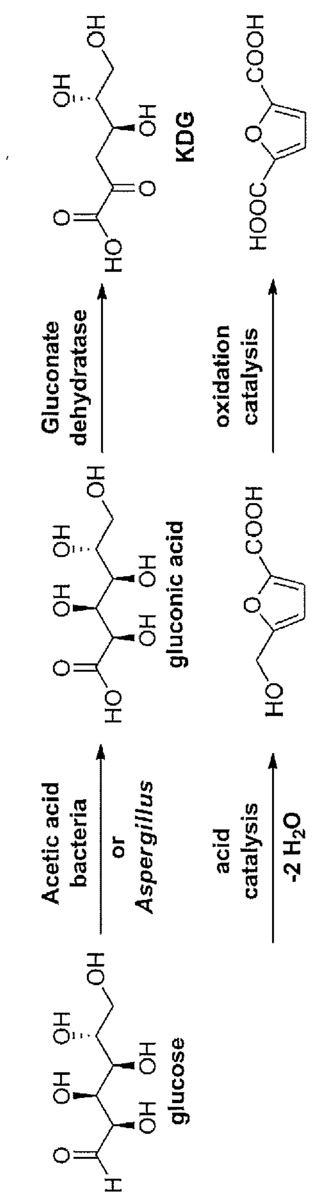
12. The method of claim 10, wherein the keto-intermediate product is 2-keto-3-deoxygluconic acid; or wherein the keto-intermediate product is 5-ketogluconic acid; or wherein the keto-intermediate product is selected from the group consisting of 3-deoxy-D-fructose, D-lyxo-5-hexulosonic acid and 4-deoxy-5-ketogalactactaric acid or any combination thereof.

13. The method of claim 10, wherein oxidation of the monosaccharide occurs microbially; or wherein oxidation of the monosaccharide occurs enzymatically.

14. The method of claim 10, wherein dehydration of the oxidized product comprises contacting the oxidized product with an enzyme to provide keto-intermediate product.

15. The method of claim 14, wherein the enzyme is selected from the group consisting of Galactonate dehydratases having the classification E.C. 4.2.1.6, Altronate dehydratases having the classification E.C. 4.2.1.7, Mannonate dehydratases having the classification E.C. 4.2.1.8, Dihydroxyacid dehydratases having the classification E.C. 4.2.1.9, Gluconate dehydratases having the classification E.C. 4.2.1.39, Glucarate dehydratases having the classification E.C. 4.2.1.40, Galactarate dehydratases having the classification E.C. 4.2.1.42, D-Fuconate dehydratases having the classification E.C. 4.2.1.67, L-Fuconate dehydratases having the classification E.C. 4.2.1.68, Xylonate dehydratases having the classification E.C. 4.2.1.82, Gluconate/galactonate dehydratases having the classification E.C. 4.2.1.140, and L-Galactonate dehydratases having the classification E.C. 4.2.1.146; or wherein the enzyme is selected from the group consisting of gluconate dehydratase and dihydroxyacid dehydratase or a combination thereof.

16. The method of claim 1, wherein the furan derivative is 5-hydroxymethyl-2-furoic acid; or wherein the furan derivative is 5-formyl-2-furoic acid.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or
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Gluconate dehydratase
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acid catalysis
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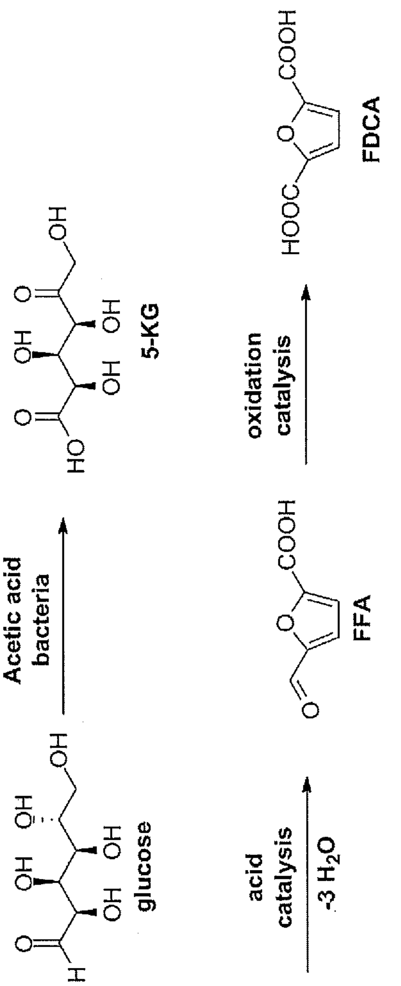
HMFA
oxidation catalysis
FDCA

Fig. 1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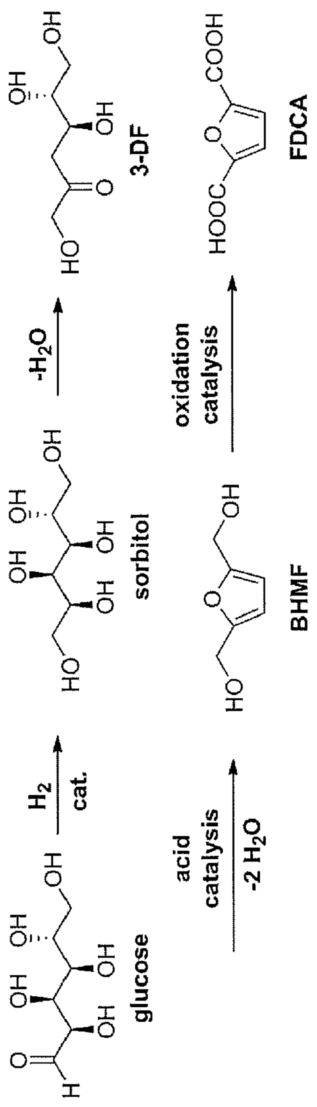
FDCA

Fig. 2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oxidation catalysis
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COOH
FDCA

Fig. 3

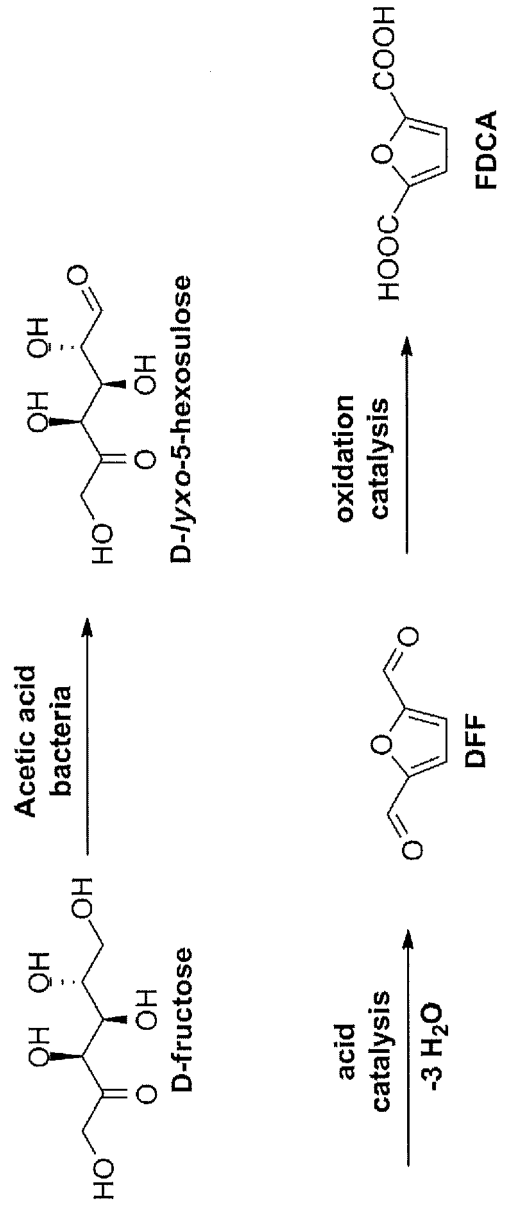
D-fructose
Acetic acid bacteria
D-lyxo-5-hexosulose
acid catalysis
-3 H_2O
DFF
oxidation catalysis
FDCA
HOOC
COOH

Fig. 4

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EUROPEAN SEARCH REPORT

Application Number
EP 20 18 2712

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Place of search	Date of completion of the search	Examiner
Munich	23 October 2020	Gavriliu, Daniela

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